HARBOR: A Phase 2/3 Study of BLU-263 in Patients With Indolent Systemic Mastocytosis and Monoclonal Mast Cell Activation Syndrome

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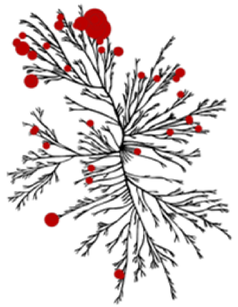
Introduction

- Systemic mastocytosis (SM) is a myeloid neoplasm driven by the *KIT* D816V mutation in ~95% of cases[1–3]
- The *KIT* D816V mutation leads to increased accumulation of aberrant mast cells (MCs) in bone marrow, skin, gastrointestinal tract, and other organs, which can result in chronic and debilitating symptoms that negatively impact quality of life[3]
- Most patients with SM have non-advanced forms, including the World Health Organization (WHO)-classified variant of indolent SM (ISM)
  - MC infiltration in the skin is common in ISM but is not always present
  - Approximately 5% of patients with ISM progress to advanced forms of SM associated with poor survival[4]
- Monoclonal mast cell activation syndrome (mMCAS) is a rare MC disease which does not meet the WHO diagnostic criteria for SM but is defined by the presence of the *KIT* D816V mutation[5,6]
- Despite conventional therapy, there remains an unmet need in ISM and mMCAS to reduce symptom burden and/or alter the disease course[7]
- Currently, no KIT D816V-targeted therapies are approved for ISM and mMCAS
- BLU-263 is a novel, oral, next-generation investigational tyrosine kinase inhibitor (TKI) with high selectivity and potency for KIT D816V, and minimal central nervous system penetration[8]



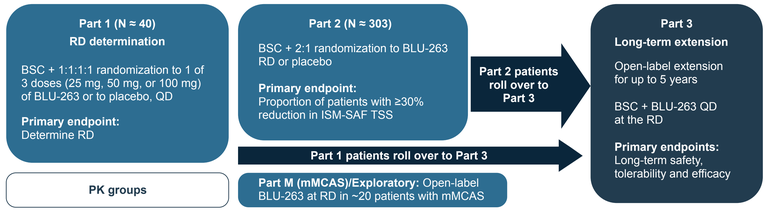
BLU-263 kinome

- Preclinical data has demonstrated the high potency of BLU-263 for KIT D816V in both biochemical (Kd=0.24 nM) and cellular (IC_{50}=4.3 nM) assays
- Phase 1 findings demonstrated the safety of BLU-263 across all tested doses in healthy participants, and the corresponding pharmacokinetics were linear across the dose ranges in single ascending and multiple ascending dose cohorts, with the half-life supporting once-daily (QD) dosing[8]

Study objectives and design

- The phase 2/3 HARBOR trial (NCT04910685) is a randomized, double-blind, placebo-controlled study designed to determine the recommended dose (RD) of BLU-263 and to evaluate the safety, tolerability, and efficacy of BLU-263 in patients with ISM or mMCAS whom have not previously received any targeted KIT inhibitor therapy and in whom symptoms are not adequately controlled by best supportive care (BSC)
- Objective measures of BLU-263 efficacy include changes from baseline in bone marrow MC burden, serum tryptase, and peripheral blood *KIT* D816V variant allele fraction
- All patients will also be receiving BSC
- In Part 1, patients may receive placebo or BLU-263 at 25 mg, 50 mg or 100 mg QD. Once an RD is determined from Part 1, patients will roll over to Part 3 to evaluate open-label, long-term safety and efficacy of BLU-263
- In Part 2, patients receive BLU-263 or placebo at the recommended Part 2 dose for 24 weeks to evaluate the proportion of patients achieving a meaningful reduction in symptom scores. Patients in Part 2 will also roll over to the open-label Part 3 extension
- Two pharmacokinetic (PK) groups receiving BLU-263 in an open-label fashion, prior to or concurrent with Part 1 and Part 2, are planned to better characterize the PK and safety of BLU-263 in patients with ISM with varying symptom burden
- In the exploratory, open-label Part M, patients with mMCAS will receive BLU-263 RD for up to 5 years

HARBOR study design



BSC, best supportive care; ISM-SAF, ISM Symptom Assessment Form; mMCAS, monoclonal mast cell activation syndrome; PK, pharmacokinetic; QD, once-daily; RD, recommended dose; TSS, total symptom score.

Key eligibility criteria

Inclusion criteria

- ≥18 years of age (≥16 years allowed if permitted by local regulations)
- ECOG performance status is 0–2
- Moderate-to-severe symptoms based on the ISM-SAF mean total symptom score (Part 1)
- Pathologically and centrally confirmed diagnosis of ISM by BM biopsy and central review of B- and C-findings according to WHO diagnostic criteria (Part 1, Part 2, PK groups); or of mMCAS by BM biopsy[a] (Part M)
- Failure to achieve adequate symptom control for ≥1 baseline symptoms (Part 1, Part 2, PK groups)[b]
- BSC for ISM symptom management and ISM symptomatic therapies[c] must be stable for ≥14 days prior to starting screening procedures (Part 1, Part 2, PK groups)
- Patients must have symptoms consistent with mast cell activation (despite BSC) in at least 2 organ systems (Part M)[d]

Exclusion criteria

- Patients have been diagnosed with other SM subclassifications or organ damage C-findings attributable to SM[e]
- Diagnosis of another myeloproliferative disorder (e.g., myelodysplastic syndrome, myeloproliferative neoplasm)
- Prior treatment with any targeted KIT inhibitors[f]
- Received the following therapy prior to first dose of the study drug:
  - Radiotherapy or psoralen and ultraviolet A therapy <14 days before beginning the screening assessments
  - Any hematopoietic growth factor <14 days before beginning the screening assessments
- Patient is currently receiving an investigational agent in another interventional study
- Patient has a history of a primary malignancy that has been diagnosed or required therapy within 3 years prior to the study[g]

[a]An archival biopsy may be used if completed within the past 12 months. [b]Using ≥2 of the following symptomatic therapies: H1 blockers, H2 blockers, proton-pump inhibitors, leukotriene inhibitors, cromolyn sodium, corticosteroids, omalizumab. [c]No new medications ≥14 days before beginning the 14-day eligibility screening period. [d]Characterized by cutaneous flushing, tachycardia, syncope, hypotension, diarrhea, nausea, vomiting and gastro-intestinal cramping, and serum blood tryptase (sBT) levels above 8 ng/mL OR Severe (Ring and Messmer grading ≥II), recurrent anaphylaxis, including but not limited to hymenoptera venom, drug or food, regardless of sBT levels. [e]World Health Organization SM subclassification (cutaneous SM only, smoldering SM, SM with associated hematologic neoplasm of non-MC lineage, aggressive SM, mast cell leukemia, mast cell sarcoma). [f]Masitinib and midostaurin not considered targeted KIT inhibitors. [g]The following prior malignancies are not exclusionary: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, and completely resected carcinoma in situ of any site.
BM, bone marrow; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; ISM-SAF, ISM Symptom Assessment Form; MC, mast cell; SM, systemic mastocytosis.

Key study endpoints

Primary endpoints

- **Part 1**
  - Determination of RD
  - PK and PD
- **Part 2**
  - Proportion of patients who achieve a ≥30% reduction in ISM-SAF TSS from baseline at Week 25
- **Parts 1 and 3**
  - Safety and tolerability
  - Mean change in ISM-SAF TSS[a,c]

Secondary endpoints

- **Part 1**
  - Mean change in ISM-SAF Individual Symptom Scores[a]
- **Part 2**
  - ≥50% reduction in measures of MC burden[b]
  - Mean change in ISM-SAF
- **Parts 1 and 2**
  - Mean change in measures of MC burden[a,b]
- **Part 3**
  - Mean change in serum tryptase and *KIT* D816V VAF in the blood[c]
  - Mean change in ISM-SAF Individual and Lead Symptom Scores from baseline

Exploratory endpoints

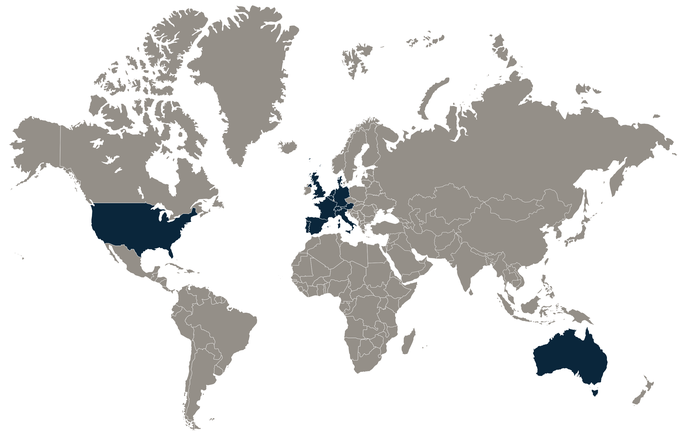
- **Part M (mMCAS)**
  - Proportion of patients achieving ≥30% reduction in MC-QoL
  - ≥50% reduction and mean change in measures of MC burden[b]

[a]From baseline at Week 13 (Part 1). [b]Serum tryptase, *KIT* D816V VAF, and BM MCs. [c]From BLU-263 baseline (Part 3).
MC-QoL, Mastocytosis Quality of Life Questionnaire; VAF, variant allele fraction.

Enrollment and current status

- Recruitment has started and enrollment is planned globally at approximately 70 sites in 15 countries worldwide

Current study sites



Summary

- The phase 2/3 HARBOR study is designed to seamlessly assess the safety, efficacy, and tolerability of BLU-263 as a potential treatment option to reduce symptom burden for patients with ISM and mMCAS and is currently recruiting for Part 1 and PK Groups
- For more information visit

https://www.blueprintclinicaltrials.com/en-us/study/harbor

https://clinicaltrials.gov/ct2/show/NCT04910685

- To learn more about our clinical trials, visit blueprintclinicaltrials.com or contact us in the USA at medinfo@blueprintmedicines.com or 1-888-BLU-PRNT (1-888-258-7768), and in Europe at medinfoeurope@blueprintmedicines.com or +31 85 064 4001

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